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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/020,674	10/30/2001	Hiroaki Yamamoto	06501- 092001 / D1-A0009-	1427

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EXAMINER
PAK, YONG D

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/020,674	YAMAMOTO ET AL.	
	Examiner	Art Unit	
	Yong Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *5-7 and 10-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6 & 8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The preliminary amendment filed on April 19, 2002, amending the specification, has been entered.

Claims 1-23 are pending.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-4 and 8-9) in Paper No. 10 is acknowledged.

Claims 5-7 and 10-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10.

Claim Objections

Claim 8 is objected to as being dependent upon a non-elected base claim, and should be rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 8 has been interpreted to include all the limitations of its base claim and any intervening claims.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-4 and 8-9 are rejected under 35 U.S.C. 101 because the claimed invention is directed to a non-statutory subject matter. Claims 1-4 and 8-9 read on a product of nature. This rejection can be overcome by amending the claims as "An isolated (R)-2,3-butanediol...", for example.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-2 are drawn to a (R)-2,3-butanediol dehydrogenase having the enzymatic and physical properties listed in claims 1-2. Therefore, these claims are drawn to a genus of (R)-2,3-butanediol dehydrogenase, with any structure and from any source. Even though claim 3 limits the source of the (R)-2,3-butanediol dehydrogenase to the genus of Pichia, the specification only teaches <u>one</u> representative species, SEQ

ID NO:2, from *Pichia angusta* having the properties recited in claims 1 and 2. One representative species is not enough to describe the whole genus and there is no evidence on the record of the relationship between the structure of a *P. angusta* (R)-2,3-butanediol dehydrogenase and the structure of a (R)-2,3-butanediol dehydrogenase from another source. Therefore, the specification fails to describe other representative species of the genus of (R)-2,3-butanediol dehydrogenase having the properties listed in claims 1-2.

Claim 8, which ultimately depends from claim 5, is drawn to a (R)-2,3-butanediol dehydrogenase from any source wherein one or more amino acids of SEQ ID NO:2 is be modified by deletion, addition, insertion, or substitution. Since there is no limit to structure or source of the polypeptide, the claim encompasses a genus of molecules described by the function of having (R)-2,3-butanediol dehydrogenase activity. The single species (R)-2,3-butanediol dehydrogenase from *P. angusta* of SEQ ID NO:2 is insufficient to describe the whole genus containing a vast number and combinations of amino acid deletions, insertions, additions, or substitutions. The specification fails to place limitations on the (R)-2,3-butanediol dehydrogenase structure or disclose which amino acid(s) of SEQ ID NO:2 can be safely modified and still impart (R)-2,3-butanediol dehydrogenase activity. Therefore, the specification fails to describe other representative species from other sources or by identifying characteristics or structural properties other than the functionality of being a (R)-2,3-butanediol dehydrogenase.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention

in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 1-3 and 8.

Claims 1-3 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the (R)-2,3-butanediol dehydrogenase of SEQ ID NO: 2, does not reasonably provide enablement for (R)-2,3-butanediol dehydrogenase different from SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Despite knowledge in the art for the isolation of amino acids, the specification fails to provide guidance regarding how to isolate other (R)-2,3-butanediol dehydrogenase whose sequence is different from SEQ ID NO:2. Therefore, the breadth of these claims is much larger than the scope enable by the specification.

The predictability as to the level of conservation between the disclosed sequences and those of other carbonyl reductase is extremely complex. While

recombinant techniques are available, it is not routine in the art to screen large numbers of amino acids where the expectation of obtaining similar sequences is unpredictable. The amino acid sequence determines the structural and functional properties of an enzyme. Knowledge of which sequences can be altered or removed and still result in similar protein activity is well outside the realm of routine experimentation.

The specification, as discussed above which places no limit to the source or structure (R)-2,3-butanediol dehydrogenase, does not support the broad scope of the claims because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting (R)-2,3-butanediol dehydrogenase activity; (B) the general tolerance to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for substitutions, deletions, insertions/additions or multiple modifications, as encompassed by the instant claims. Also, the positions within a protein's sequence

where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

Therefore, one of ordinary skill would require guidance in order to make (R)-2,3-butanediol dehydrogenase different from SEQ ID NO:2 in a manner reasonable correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1-3 and 8, part (c) of claim 1 is confusing. The phrase is confusing to read and the rejection can be overcome by amending the claim as "the dehydrogenase has a specific activity of 100U/mg or greater when purified", for example.

Claim Rejections - 35 USC § 102

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claims 1 and 8 are rejected under 35 U.S.C. 102(a) as being anticipated by Gonzalez et al.

Gonzalez s et al. (form PTO 892) teach a (R)-2,3-butanediol dehydrogenase that produces (R)-acetoin by acting on (2R,3R)-2,3-butanediol using a NAD as a coenzyme and produces (2R,3R)-2,3-butanediol by reducing 2,3-butanedione using a reduced from of NAD as a coenzyme (pages 35876 and 35881-35884). The dehydrogenase of Gonzalez et al. preferentially oxidizes a hydroxyl group of 2,3-butanediol in the (R) configuration and has a specific activity of 100U/mg or higher when purified (pages 35876 and 35881-35884).

Further, the (R)-2,3-butanediol dehydrogenase of Gonzalez et al. can be construed as a polypeptide of SEQ ID NO:2 wherein one or more amino acid residues are substituted, deleted, inserted and/or added.

Therefore, the teachings of Gonzalez et al. anticipate claims 1 and 8.

Claims 1 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Heidlas et al.

Heidlas et al. (form PTO 1449) teach a (R)-2,3-butanediol dehydrogenase that produces (R)-acetoin by acting on (2R,3R)-2,3-butanediol using a NAD as a coenzyme and produces (2R,3R)-2,3-butanediol by reducing 2,3-butanedione using a reduced from of NAD as a coenzyme (page 267). The dehydrogenase of Heidlas et al. preferentially oxidizes a hydroxyl group of 2,3-butanediol in the (R) configuration (pages 267 and 271-272). It is well known in the art that the use of high performance columns, such as Resource Q (Pharmacia Biotech and Gonzalez et al.), the purity of enzymes can be increased, increasing the specific activity of the enzyme. The dehydrogenase of Heidlas et al. can have a specific activity of 100U/mg or higher when purified with various purification steps well known and practiced in the art.

Further, the (R)-2,3-butanediol dehydrogenase of Heidlas et al. can be construed as a polypeptide of SEQ ID NO:2 wherein one or more amino acid residues are substituted, deleted, inserted and/or added.

Therefore, the teachings of Heidlas et al. anticipate claims 1 and 8.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 8 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3-4 of copending Application No. 10/147,003. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are claiming common subject matter, as follows: a (R)-2,3-butanediol dehydrogenase that produces (R)-acetoin by acting on (2R,3R)-2,3-butanediol using a NAD as a coenzyme and produces (2R,3R)-2,3-butanediol by reducing 2,3-butanedione using a reduced from of NAD as a coenzyme (page 267).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 703-308-9363. The examiner can normally be reached on 8:00 A.M. to 4:30 P.M weekdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Yong Pak
Patent Examiner

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